



COMPARISON OF BLOOD PRESSURE IN HYPERTENSIVE PATIENTS WITH MONOTHERAPY AND COMBINATION ANTIHYPERTENSIVE THERAPY

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Abstract

Background: Hypertension is a cardiovascular risk factor that is closely related to the patient's systolic and diastolic blood pressure profile. **Objective:** This study aims to determine the comparison of systolic and diastolic blood pressure profiles using antihypertensives in patients with cardiovascular risk factors. **Method:** Conducted in the period August-December 2021 on 83 patients who met the inclusion criteria, namely outpatients diagnosed with hypertension with cardiovascular risk factors, adult patients over 18 years of age, a medical record sheet, and a written prescription in full. Data analysis used the Kruskal Wallis test. **Results:** Shows a p value of $0.02 < 0.05$ that there is a difference in systolic and diastolic blood pressure when using antihypertensive monotherapy or combination. The use of antihypertensive monotherapy is able to achieve the target of reducing systolic and diastolic blood pressure, namely amlodipine by -42.4mmHg/-11.7mmHg. Meanwhile, the combination antihypertensive that provides maximum results is a combination of 2 drugs, namely Candesartan + Hydrochlorthiazide which produces a reduction of -42.64 mmHg/-16.09 mmHg; a combination of 3 drugs: Amlodipine + Candesartan + Hydrochlorthiazide resulted in a reduction of -49 mmHg/-19.1 mmHg. **Conclusion:** There are differences in the profile of reducing systolic and diastolic blood pressure when using monotherapy and combination antihypertensives. The choice of monotherapy and combination can provide benefits in reducing blood pressure, tolerability and the level of compliance with the drugs consumed. Rational dose selection and drug selection in hypertensive patients is an important part in achieving successful therapy and preventing drug related problems, so pharmacists need to always monitoring blood pressure profiles as a form of monitoring the effectiveness of existing antihypertensive drugs consumed by patients.

Keywords: Hypertension, Cardiovascular, Blood Pressure



Background

Hypertension is the number one risk factor for death globally, affecting more than 1 billion people. Hypertension accounts for about half of all heart disease and stroke-related deaths worldwide. Hypertension does not cause symptoms, so it is often called the silent killer. The European Heart Journal explains that the standard for blood pressure is 120/80 mmHg, while a person is declared to have grade 1 hypertension if his blood pressure is $> 140/90$ mmHg (Mancia *et al.*, 2018).

The Joint National Committee 8 recommends that the blood pressure target to be achieved for age <60 years is $<140/90$ mmHg and the blood pressure target for age 60 years is $<150/90$ mmHg and for all ages with chronic kidney failure with or without diabetes is $< 140/90$ mmHg (James *et al.*, 2014). The optimal blood pressure target is still a matter of debate. The SPRINT trial demonstrated a reduction in cardiovascular outcomes (including death) with unsupervised intensive care of a systolic blood pressure target of <120 mmHg, compared with a target systolic blood pressure of <140 mmHg. This reduction is offset by an increase in side effects, including electrolyte abnormalities, worsening renal function and hypotension (Brouwers *et al.*, 2021).

Antihypertensive treatment can use monotherapy or a combination (James *et al.*, 2014). Combination therapy is recommended in patients with blood pressure $>150/95$ mmHg (MacDonald *et al.*, 2017). American Heart Association guidelines recommend ACE inhibitors, ARBs, calcium channel blockers, and thiazides as first-line agents (Brouwers *et al.*, 2021). Uncontrolled hypertension is very common worldwide and based on epidemiological data, accounts for a large number of deaths and disabilities globally (Rea *et al.*, 2018). High blood pressure is a major risk factor for cardiovascular disease-related events, the higher the blood pressure the greater the chance of heart attack, heart failure, stroke and kidney disease (Dorresteijn *et al.*, 2012). Cardiovascular complications are caused by several reasons such as low effectiveness of antihypertensive monotherapy, irrational combinations and patient medication non-adherence (Düsing *et al.*, 2017).

One of the important things in the choice of combination therapy is the value of lowering blood pressure. In addition, combining drugs with complementary mechanisms of action may provide benefits beyond lowering blood pressure, such as increased tolerability, and thus higher rates of adherence to the prescribed drug compared to increasing the dose of a single agent (Düsing *et al.*, 2017). Inappropriate use of antihypertensive drugs can cause a spectrum of toxicity, failure of treatment therapy, high treatment costs, complications to patient death, as well as hampering the quality of health services. So that the strategy for selecting antihypertensive drugs should be carried out according to therapeutic guidelines (Sonya.A.P, Bagus, 2019). In a study conducted in Semarang-Indonesia which analyzed the cost-effectiveness of combined drug therapy, it was shown that ACE inhibitors and diuretics are the most widely used antihypertensive drug classes, because ACE inhibitors are more or less effective than other groups, and are safe because they do not cause side effects. Metabolic in long-term use, and diuretics may enhance the action of other antihypertensive drugs. So that if the two are combined, it produces a high effectiveness value and the best cost-effectiveness value (Esther *et al.*, 2016). Based on the above, the researchers wanted to conduct a study on the comparison of the use of single and combination antihypertensives on the profile of lowering blood pressure in patients with cardiovascular risk factors.

Materials and Methods

This study used an analytical observational design with a retrospective cohort method that was observed for three months. This study was conducted at the Lamongan Health Facility, namely, in August-December 2021 amounted to 83 patients. The sample of this study was all hypertension patients with cardiovascular risk factors at the Lamongan "X" Clinic who were included in the inclusion criteria. The inclusion criteria of this study were outpatients diagnosed with hypertension with cardiovascular risk factors, adult patients over 18 years of age, medical record sheet, and a

written prescription in full. Data obtained from medical records and medications then identified the profile of the decrease in blood pressure on using single and combination antihypertensives. Furthermore, data analysis using the Kruskal Wallis test. This research has an ethics certificate issued by the University of Muhammadiyah Lamongan with No. 225/EC/KEPK-S2/08/2021.

Result and Discussion

Based on the study's results (Table I), the majority of hypertensive patients were female, 74.70%, with the most dominant age range being 55-64 years, as many as 36 patients (43,38%). With increasing age, the arterial walls will experience thickening caused by the accumulation of collagen in the muscle layer, resulting in blood vessels narrowing and becoming stiff so that, in the end, the elasticity of blood vessels decreases. Cardiovascular diseases such as hypertension occur with age due to a decrease in the elasticity of the arterial walls and stiffness in the systemic blood vessels due to aging. With increasing age, individuals who have an unhealthy lifestyle will suffer from atherosclerosis, which can cause an increase in systolic and diastolic blood pressure. With age, blood pressure increases and arterial walls will experience thickening due to the accumulation of collagen in the muscle layer, so blood vessels narrow and become stiff (S. A. Khan, 2021). Another characteristic seen from the highest risk of cardiovascular factors in hypertensive patients is dyslipidemia, 77.11%. After that, based on **Table II**, there are single and combination antihypertensives. Single antihypertensives are Amlodipine, which is widely used (12.05%), while combination antihypertensives are combinations of candesartan and thiazides (13.25%). The results of the decrease in the patient's systolic blood pressure (SBP) and diastolic (DBP) can be seen in **Table I**.

Table I. Characteristics of Patient Hypertension

Characteristics	F	%
Gender		
Male	21	25,30
Female	62	74,70
Age (years)		
35-44	3	3,61
45-54	7	8,43
55-64	36	43,38
65-74	25	30,12
≥75	12	14,46
Body Mass Index (kg/m²)		
Normal (18,5-22,9)	2	2,41
Overweight (23,0-24,9)	10	12,05
Obese (≥25,0)	71	85,54
Comorbidities		
Dyslipidemia	44	53,01
Diabetes Mellitus	18	21,69
Coronary heart disease	14	16,87
Stroke	7	8,43
Total	83	100

Table II. Types of Use of Antihypertensive Drugs

Single Antihypertensive	F	%
Ca Channel Blocker (Amlodipin)	10	12,05
Beta Blocker (Bisoprolol)	1	1,20
Angiotension Receptor Blocker (Candesartan)	6	7,23
Angiotension Converting Enzyme Inhibitor(captopril)	3	3,61
Diuretik (Thiazid)	1	1,20
Diuretik (Furosemid)	2	2,41
Combination Antihypertensive	F	%
AMLODIPIN+BISOPROLOL	7	8,43
AMLODIPIN+CANDESARTAN	7	8,43
AMLODIPIN+BISOPROLOL+CAPTOPRIL	1	1,20
AMLODIPIN+CANDESARTAN+BISOPROLOL	4	4,82
AMLODIPIN+CANDESARTAN+FUROSEMID	10	12,05
AMLODIPIN+CANDESARTAN+FUROSEMID+BISOPROLOL	3	3,61
AMLODIPIN+CAPTOPRIL	4	4,82
AMLODIPIN+FUROSEMID	2	2,41
AMLODIPIN+FUROSEMID+CAPTOPRIL	1	1,20
AMLODIPIN+FUROSEMID+CAPTOPRIL+BISOPROLOL	1	1,20
CANDESARTAN+BISOPROLOL	2	2,41
CANDESARTAN+FUROSEMID	11	13,25
CANDESARTAN+FUROSEMID+CAPTOPRIL	1	1,20
CAPTOPRIL+BISOPROLOL	1	1,20
THIAZID +BISOPROLOL	1	1,20
FUROSEMID+CANDESARTAN+BISOPROLOL	4	4,82
Total	83	100

Table III. Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) Results Data for Hypertensive Patients

Single Antihypertensive	Decrease SBP/DBP (mmhg)
Amlodipin	42,4 / 11,07
Bisoprolol	30/ 20
Candesartan	40,84/ 17,17
Captopril	30,34 / 15,33
Diuretik Furosemid	70 / 0
Diuretik Thiazid	65 / 15
Combination Antihypertensive	Decrease SBP/DBP (mmhg)
AMLODIPIN+BISOPROLOL	49,71 / 17,14
AMLODIPIN+CANDESARTAN	50,427 / 36
AMLODIPIN+BISOPROLOL+CAPTOPRIL	100 / 30
AMLODIPIN+CANDESARTAN+BISOPROLOL	55 / 16,5
AMLODIPIN+CANDESARTAN+ HYDROCHLORTHIAZID	49 / 19,1
AMLODIPIN+CANDESARTAN+FUROSEMID+BISOPROLOL	53,34 / 16,66
AMLODIPIN+CAPTOPRIL	57,25 / 14,75
AMLODIPIN+THIAZID+CAPTOPRIL	51,5 / 17,5

AMLODIPIN+FUROSEMID	120 / 120
AMLODIPIN+FUROSEMID+CAPTOPRIL+BISOPROLOL	40 / 10
CANDESARTAN+BISOPROLOL	45 / 20
CANDESARTAN+HYDROCHLORTHIAZID	42,64 / 16,09
CANDESARTAN+FUROSEMID+CAPTOPRIL	60 / 30
CAPTOPRIL+BISOPROLOL	66 / 20
FUROSEMID+CANDESARTAN+BISOPROLOL	47,5 / 15

Most of the patients who suffer from hypertension are female (74.70%), this is due to a decrease in estrogen which has an impact on cardiovascular where there is a decrease in the elasticity of blood vessels. Women are also at risk of hypertension after menopause, namely age > 45 years. In menopausal women, low levels of High Density Lipoprotein (HDL) and high Low Density Lipoprotein (LDL) will affect the process of atherosclerosis and result in high blood pressure (Sabbatini and Kararigas, 2020).

Based on the results of research on patient characteristics data based on comorbid types (comorbidities), that hypertensive patients who have a risk of cardiovascular disease (CVD) tend to be obese (85.54%). Obesity can contribute to hypertension and also the prevalence of dyslipidemia (53.01%) and diabetes mellitus (DM) of 21.69%. It was also mentioned in the study (Saleem *et al.*, 2019) that dyslipidemia was significantly higher in female DM patients than male. The existence of CVD risk requires special monitoring of hypertension therapy management to anticipate and prevent the severity of CVD that can occur.

Pharmacological management of antihypertensives begins with monotherapy with a target of reducing systolic blood pressure (SBP) BP of about 7-13 mmHg and diastolic blood pressure (DBP) of around 4-8 mmHg. If the blood pressure target is not achieved within one month of treatment, it can be done by increasing the initial drug dose or adding other drug classes from first and second line therapy to minimize side effects of drug interactions. The single most dominant antihypertensive use in this study was Amlodipine. Amlodipine has vasculoselective properties, antioxidants, has a relatively low oral bioavailability, has a long half-life, and slow absorption, thus preventing a sudden drop in blood pressure. In a study in India, single amlodipine administered to hypertensive patients aged 45-65 years achieved a reduction in SBP and DBP of 25.5% and 13.7%, so that amlodipine is considered effective in controlling blood pressure in patients with essential hypertension (M. Y. Khan *et al.*, 2020). Amlodipine has also been shown to have good efficacy and safety in reducing the incidence of CVD in a randomized controlled trial (RCT), thus making amlodipine often recommended as a first-line antihypertensive agent (Fares *et al.*, 2016).

The effectiveness of antihypertensive drugs can be seen from the decrease in the patient's blood pressure. Clinical data on blood pressure is one of the main indicators of the success of antihypertensive treatment towards achieving blood pressure targets (Utami *et al.*, 2020). In the blood pressure drop profile table (Table III), Amlodipine Single Antihypertensive experienced a decrease in SBP and DBP by -42.4 mmhg/-11.7 mmhg. The results of the greatest single antihypertensive SBP reduction was in the use of diuretics of 70 mmHg, but it was not accompanied by a persistent decrease in DBP, there was no change in the profile of DBP reduction. Thus, the single antihypertensive that relatively gave significant results in reducing the blood pressure profile was amlodipine. In a systematic review study evaluating the decrease in blood pressure from the use of a class of diuretic therapy including furosemide, it was stated that there was no clinically significant difference in the reduction of SBP and DBP between drugs in the loop diuretic class (Musini *et al.*, 2015).

The use of combination antihypertensives is generally also carried out to achieve therapeutic goals, more effective lowering of blood pressure, reducing side effects to improve patient compliance. In patients with systolic blood pressure > 20 mmHg and/or diastolic blood pressure > 10 mmHg and who are at risk of CVD, it will be necessary to give antihypertensive combinations of two to 3

drugs at once or even more. This result can be seen in the study that the dominant combination antihypertensive used was a combination of (Amlodipine+Candesartan+Hydrochlorthiazide) and ARB+Thiazid (Candesartan+hydrochlorthiazide). The combination of candesartan + hydrochlorthiazide has better cardiovascular tolerance and lowers blood pressure than monotherapy and can therefore lead to better patient adherence to medication. The strong vasodilator properties of amlodipine, able to provide blood pressure lowering results that are more effective in the use of a combination of 3 drugs than the combination of 2 drugs. The combination of CCB and ARB is a rational combination to use because it is able to buffer the Renin Angiotensin Aldosterone System (RAAS) activation (Fares *et al.*, 2016).

Based on the table of the average difference between the decrease in SBP and DBP (Table II) it can be seen that the combination of 3 drugs: Amlodipine+Candesartan+Hydrochlorthiazide resulted in a decrease of -49/-19,1 mmHg. Combination of 2 drugs : Candesartan + Hydrochlorthiazide resulted in a decrease in -42,64/-16,09 mmHg. Likewise, in a multicentre study, RCT, which was conducted in Japan for 12 months, stated that the combination of 2 drugs between CCB + ARB and a combination of 3 drugs: CCB + ARB + diuretic produced the same efficacy in reducing SBP and DBP. Both types of combination therapy can be used safely and effectively in patients with uncontrolled hypertension with standard doses of ARBs and CCBs. There was no significant difference in the variability of SBP, DBP, or CVD in each control period of patients. These results indicate that both types of combination treatment have the same effectiveness in controlling BP blood pressure and do not have a significant impact on the variability of blood pressure reduction (Nakagawa *et al.*, 2020).

Dosage selection and rational drug selection in hypertensive patients are an important part in achieving therapeutic success (therapeutic outcomes) and preventing drug related problems (DRP). The type of DRP in the use of antihypertensives that often occurs is drug interactions. In a cross-sectional study in Lamongan from a total of 194 outpatients, there was a 56.7% risk of potential drug interactions with moderate severity (93.0%), and categories based on the mechanism of pharmacodynamic interactions that could occur (61.2%) (Utami and Octavia, 2022).

Comparison of antihypertensive therapy with lowering blood pressure can be seen through the Kruskal Wallis non-parametric test. In the results of the Kruskal Wallis test, the asymp.sig value was obtained (<0.05), which means that there is a significant difference between the difference in pre and post systolic blood pressure using antihypertensive therapy.

Conclusion

The single antihypertensive that gives maximum results in reducing blood pressure in patients with Cardiovascular Risk Factors is Amlodipine with a maximum decrease in SBP and DBP of -42.4mmhg/-11.7mmhg. The combination of antihypertensives to reduce blood pressure that gives maximum results is a combination of 2 drugs: Candesartan + Hydrochlorthiazide which results in a decrease of -42.64/-16.09 mmHg; a combination of 3 drugs: Amlodipine+ Candesartan+ Hydrochlorthiazide resulted in a decrease of -49/-19.1 mmHg.

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